REMARKS

Claims 1-3, 7-10, and 18, as amended, and new claims 32-41 appear in this application for the Examiner's review and consideration. Claims 4-6 and 11-17 have been cancelled. Claims 19-31 have been withdrawn by the examiner as directed to non-elected subject matter. Applicants fully reserve their rights to prosecute the subject matter of any cancelled claim in one or more continuation, continuation-in-part, or divisional applications. The claims have been amended to more particularly point out the claimed subject matter and to correct inadvertent minor spelling and editorial errors, but no new matter has been added. New claims 32-41 are supported in the withdrawn claims.

Claims 1-18 stand rejected under 35 U.S.C. § 103(a) as rendered obvious over U.S. Patent No. 4,053,617 to Eichenberger *et al.* ("the '617 patent") in view of U.S. Patent No. 6,569,463 to Patel *et al.*, ("the '463 patent") for the reasons set forth on pages 4-7 of the Office Action. Applicants respectfully traverse.

The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that claimed subject matter should be carried out and would have a reasonable likelihood of success. *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988). As the Examiner is well aware, in order to form a proper basis for a rejection under 35 U.S.C. § 103, the prior art must provide some suggestion, either explicit or implicit, of the combination that allegedly renders a claimed invention obvious. *M.P.E.P.*, § 2142 (June 1998), *see also, Panduit Corp. v. Denisson Manufacturing Co.*, 1 U.S.P.Q.2d 1593, 1597 (Fed. Cir. 1987). The Examiner can satisfy the burden of showing obviousness of the combination only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references. *In re Sang Su Lee*, 277 F.3d 1338, 1343, 61 U.S.P.Q.2d 1430 (Fed. Cir. 2002); citing *In re Fritch*, 972 F.2d 1260, 1265, 23 U.S.P.Q.2d 1780, 1783 (Fed. Cir. 1992). The need for specificity is paramount, particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected the components for combination in the manner claimed. *Id.* The Examiner's conclusory statements do not adequately address the issue of motivation to combine; the factual question of motivation is

material to patentability, and can not be resolved on subjective belief and unknown authority. *Id.*

The '617 patent discloses 2,1,3-benzothiadiazole derivatives (including tizanidine) and formulations thereof. (The '617 patent, col. 1, ll. 5-22). The compound may be administered orally in the form of tablets, powders, granules, capsules, suspensions, syrups, and elixirs or parenterally in the form of injectable solutions or suspensions. (*Id.* at col. 2, ll. 45-48). The compositions may contain pharmaceutically inert organic or inorganic adjuvants, optionally granulation agents, binding agents, lubricants, dispersing agents, wetting agents and preservatives. (*Id.* ll. 49-53). Tablet formulations may be coated or uncoated with the coating having the purpose of delaying the disintegration and adsorption in the gastrointestinal track, thus providing a retarded effect over a longer period. (*Id.* at 62-66).

The '463 patent discloses pharmaceutical delivery systems for pharmaceutically active ingredients where the active is in a rapid dissolvable and more solubilized state, the composition includes a solid carrier, the solid carrier including a substrate and an encapsulation coat on the substrate. (The '463 patent, col. 2, ll. 17-19 and col. 3, ll. 61-66). One object of the invention is to provide solid pharmaceutical compositions having better protection of the upper gastrointestinal tract from effects of the active ingredient. (*Id.* at ll. 40-44). The active ingredient can be hydrophilic, lipophilic, amphiphilic or hydrophobic, and can be solubilized, dispersed, or partially solubilized and dispersed, in the encapsulation coating. (*Id.* col. 4, ll. 28-32). After disclosing 52 categories of active ingredients, tizanidine is mentioned as one of 199 possible active ingredients, or one of 54 most preferred ingredients. (*Id.* col. 4, l. 53 to col. 7, l. 15).

The '617 fails to render obvious the claimed method because it fails to teach compositions capable of buccal or sublingual absorption, in fact, the '617 teaches against this. While the '617 discloses a variety of formulations and elaborates on a variety of ingredients, it focuses on standardized drug delivery and not on buccally or sublingually absorbed formulations. As explained in the current application, buccal or sublingual absorption of tizanidine avoids the first pass hepatic metabolism where tizanidine undergoes degradation. The '617 patent teaches to coat the formulation as a method to avoid degradation, but this is contrary to buccal or sublingual absorption as the coating prohibits quick drug release and delays drug disintegration and adsorption in the gastrointestinal track.

Also, the '617 patent does not teach the increase in bioavailability AUC_{inf} of the claim, in fact, it cannot. The bioavailability increase is due to the novel non-standardized formulations and the buccal and sublingual absorption, which is measured against the standardized formulations such as those taught by the '617 patent. To remedy the deficiencies of the '617 patent, the Office cites the generic '463 patent, however, this is to no avail.

The '463 patent does not remedy the deficiencies of the '617 patent, as it still does not disclose or suggest formulations for buccal or sublingual absorption of tizanidine or the 10% increase in bioavailability AUC_{inf}. The '463 patent generically discloses tizanidine as one of 199 possible choices among the hydrophobic compounds, and even as a preferred compound tizanidine still is one of 54 possible choices. And while the '463 patent discloses rapidly dissolvable compositions of these many compounds, it does not disclose their buccal or sublingual formulation or absorption. Rapid dissolution cannot be equated with absorption as dissolution does not ensure absorption, it only guarantees conversion of solid to liquid but not drug transfer across mucosa lining.

Also, as discussed above, the '617 disclosed coating the formulations, likewise the '463 discloses encapsulating the active ingredient, both teachings delay drug delivery which is contrary to what is needed for buccal or sublingual absorption. The combination of references yields a standardized formulation which alone or in combination with coatings or encapsulation does not yield the buccally or sublingually absorbed tizanidine formulations used in the method of the claims.

Accordingly, the rejection of claims 1-3, 7-10, and 18 under 35 U.S.C. § 103(a) as rendered obvious by the '617 patent in view of the '463 patent cannot stand and should be withdrawn.

Accordingly, it is believed that claims 1-3, 7-10, 18, and 32-41 are now in condition for allowance, early notice of which would be appreciated.

If any outstanding issues remain, the examiner is invited to telephone the undersigned at the telephone number indicated below to discuss the same. No fee is believed to be due for the submission of this response. Should any fees be required, please charge such fees to Kenyon & Kenyon, LLP Deposit Account No. 10-0600.

Respectfully submitted,

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